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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/475,704 | 12/30/1999 | SUSAN W. BARNETT | 1631.002 | 6738 |

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| EXAMINER | |
|---|---|
| WHITEMAN, BRIAN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/475,704 | BARNETT ET AL. | |
| | Examin r | Art Unit | |
| | Brian Whiteman | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with th correspond nce address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,24-43,49-60 and 62-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *68-73* is/are allowed.

6)☒ Claim(s) *1-10,24-43,49-60,62-67,74,75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### Final Rejection

Claims 1-10, 24-43, 49-60, and 62-75 are pending.

Applicants' traversal, the cancellation of claims 11-23, 44-48, and 61, the amendment to claims 1, 2, 67, 68, and 69, the amendment to the specification and the revised sequence listing in paper filed on 8/28/03 is acknowledged and considered.

### *Claim Objections*

Applicant is advised that should claim 49 be found allowable, claim 62 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 24-40, 42, 43, 49-60, and 62-66 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10, 24-40, 42, 43, 49-60, and 62-66, as best understood, are readable on a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4, wherein the genus of polynucleotide sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4. The as-filed specification provides sufficient description of an immunogenic HIV Gag polypeptide set forth in SEQ ID NO: 3 or 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) and fragment of SEQ ID NO: 4 (SEQ ID NO: 2). Furthermore, the as-filed specification and art of record teach that Gag proteins of HIV are necessary for the assembly of virus-like particles HIV Gag proteins are involved in many stages of the life cycle of the virus including assembly, virion manufacture after particle release, and early post-entry step in virus replication. The role of HIV Gag proteins

are numerous and complex (IDS, Freed, Virology, 1998). The specification contemplates that synthetic HIV Gag polypeptides can be measured for virus-like particle (VLP) production (page 29). The claims recite a structure (polynucleotide encoding an immunogenic HIV Gag polypeptide), but do not recite a function for the genus of polynucleotide sequences. In addition, in view of the phrase "HIV Gag polypeptide", the polypeptide has to be identical (same function) to one found in an HIV in nature. The specification does not disclose how to distinguish between natural amino acid sequence and non-natural sequence that is also at least 90% identical. One skilled can envision a sequence that is at least 90% identical to the claims SEQ ID NOs., but would be unable to determine if it was an HIV sequence that was found in nature. Thus, in view of the reasons set forth above and the numerous and complex functions of HIV Gag polypeptides, the specification does not disclose which activities correspond to the claimed genus of polynucleotides with 90% sequence identity to the claimed SEQ ID NOs or how to distinguish between natural amino acid sequence and non-natural sequence that is also 90% identical.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of polynucleotide sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polynucleotide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polynucleotide sequences that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3, or 4 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-

filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 8/28/03 have been fully considered but they are not persuasive.

With respect to Applicants' arguments that, "the claims clearly recite both the structure and the function of the recited polynucleotides," the argument is not found persuasive. The argument is not found persuasive because the specification does not provide sufficient description for a polynucleotide sequence encoding a polypeptide including an immunogenic Gag polypeptide, wherein the polynucleotide having at least 90% sequence identity to the sequence presented either in SEQ ID NO: 3 or a fragment of SEQ ID NO: 3 (SEQ ID NO: 1) and SEQ ID NO: 4 or a fragment of SEQ ID NO: 4 (SEQ ID NO: 2).

The page (page 14, lines 13-18) cited for description of the claimed function does not provide sufficient description for an immunogenic Gag polypeptide. The role of HIV Gag proteins are numerous and complex (IDS, Freed, Virology, 1998). The specification does not provide sufficient description for a nucleotide sequence having 90% sequence identity and retaining HIV Gag activity and is immunogenic. In view of the definition of immunogenic in the specification (page 14, lines 13-18), any HIV Gag polypeptide is considered immunogenic, including nucleotide sequences encoding an HIV Gag polypeptide that do not have 90% sequence identity to the claimed SEQ ID NOs. The prior art teaches two nucleotide sequences encoding an immunogenic HIV Gag polypeptide that are not 90% identical to SEQ ID NO: 4.

See US Patent 6,541,248, SEQ ID NOs: 2 and 5. There is a substantial variation between species of immunogenic HIV Gag polypeptides. In addition, a nucleotide search of SEQ ID NO: 4 (1509 nucleotides) indicates that SEQ ID NO: 3 (1479 nucleotides) is 84.6% identical to SEQ ID NO: 4. The same nucleotide search of SEQ ID NO: 4 indicates that it has 98.7% sequence identity to SEQ ID NO: 21 and 83.6% sequence identity to SEQ ID NO: 20. Furthermore, SEQ ID NO: 21 and 22 are not set forth in the claims. In addition, claim 1 recites a nucleotide sequence having at least 90% sequence identity to the sequence presented as either SEQ ID NO: 1 or SEQ ID NO: 2. In other words, the sequence claims may be larger than either SEQ ID NO:. In view of the polynucleotide sequence listed above, there is a substantial variation between species of immunogenic HIV Gag polypeptides. The specification does not provide sufficient description for an HIV Gag polypeptide that has Gag activity and is immunogenic. The specification does not provide sufficient description that one of skill in the art would recognize the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. The specification does not provide sufficient description that there is any structure/function relationship between the disclosed polynucleotide sequences and any other sequences that might be embrace by the genus.

MPEP 2163 states:

> A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. Cf. In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) (holding that a process could not render the product of that process obvious under 35 U.S.C. 103). The Federal Circuit has pointed out that under

> United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at1567, 43 USPQ2d at 1405.

Furthermore, with respect to applicants' arguments that, "the Office assertion that the specification requires that the polypeptide encoded by the claimed expression cassette be "identical" to a naturally occurring Gag polypeptide," is not found persuasive. As stated above the specification does not provide sufficient description that there is any structure/function relationship between the disclosed polynucleotide sequences and any other sequences that might be embrace by the genus. The specification recites properties (e.g., functions) of Gag proteins (page 2, lines 19-24) and generation of HIV-1 type C Gag protein coding sequences having improved expression relative to the corresponding wild-type sequences (page 25, lines 24-26, page 27, lines 4-9, page 28, lines 3-6, page 29, lines 25-27, page 35, lines 1-25). More specifically, the specification recites that, "the Gag sequences also result in improved expression of polyproteins, as well as the production of VLPs formed by the polypeptides produced from such modified coding sequences (page 28, lines 1-5)." Thus, in view of the definition of an "HIV Gag polypeptide" in the specification, the polypeptide has to be identical (same function) to one found in an HIV in nature. The specification does not provide sufficient description of complete or partial structure (e.g., nucleotides or amino acids) that is required for the claimed genus of polynucleotide sequences encoding an immunogenic HIV Gag polypeptide.

With respect to applicants' argument that, "at least six representative species are described (SEQ ID NOs: 1-4, 20 and 21)" and "the representative number of species disclosed in the specification more than adequately convey to the skilled artisan that Applicants were in possession of the precisely claimed molecules at the time the application was filed," the

argument is not found persuasive. The argument is not found persuasive because a nucleotide search of SEQ ID NO: 4 (1509 nucleotides) indicates that SEQ ID NO: 3 (1479 nucleotides) is 84.6% identical to SEQ ID NO: 4. The same nucleotide search of SEQ ID NO: 4 indicates that it has 98.7% sequence identity to SEQ ID NO: 21 and 83.6% sequence identity to SEQ ID NO: 20. This percent identity indicates that there is a substantial variation among polynucleotide sequences of the disclosed HIV Gag polypeptides. 90% of SEQ ID NO: 3 is up to 148 different nucleotides and 90% of SEQ ID NO: 4 is up to 151 different nucleotides. The as-filed specification fails to provide the essential nucleotide or amino acid residues for a representative number of sequences, wherein each sequence is composed of a polynucleotide sequence having at least 90% sequence identity to the claimed SEQ ID NO: 1, 2, 3, or 4, that has an activity of a Gag polypeptide and is immunogenic. The specification does not provide sufficient description that one of skill in the art would recognize the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. Thus, for the reasons set forth above, the as-filed specification does not provide sufficient description for a genus of nucleotide sequences with up to 151 different nucleotides (90% sequence identity) to the claimed SEQ ID NO: 4 and possesses the biological activity of an HIV Gag polypeptide and is immunogenic.

With respect to applicants' arguments that, "The office reliance of *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997) is misplaced," is not found persuasive. The argument is not found persuasive because the general concept of the cases is directed to possession of species does not

equate with possession of genus. This is the case here. Thus, the argument is not found persuasive for the reasons set forth above.

Furthermore, the declaration under 37 CFR 1.132 filed 12/19/02 is insufficient to overcome the rejection of claims 1-10, 24-43, 49-60, and 62-66 based upon 112 written description as set forth in the instant Office action because: there is a substantial variation between species of immunogenic HIV Gag polypeptides as indicated by the sequence search (see results described above) of SEQ ID NO: 4 and SEQ ID NO: 3 and SEQ ID NO: 20. The specification fails to provide the essential nucleotide or amino acid residues for a representative number of polynucleotide sequences, wherein each sequence is composed of a polynucleotide sequence having at least 90% sequence identity to the claimed SEQ ID NO: 1, 2, 3, or 4, that has an activity of an HIV Gag polypeptide and is immunogenic.

Furthermore, with respect to the assertion that "at the time the specification was filed, it was well known how to align polynucleotide sequences to determine percent identity," the specification does not provide sufficient description that there is any structure/function relationship between the disclosed polynucleotide sequences and any other sequences that might be embrace by the genus. See MPEP 2163.

Claims 1-10, 24-43, 49-60, and 62-66 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 1, 2, 3, or 4, does not reasonably provide enablement for a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag

polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention lies in the field of producing an immunogenic composition using an expression cassette comprising an HIV Gag polypeptide set forth in SEQ ID NOs: 1-4.

The specification contemplates: 1) Expression assays for the synthetic coding region of Gag and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag expression cassettes using plasmid DNA carrying the synthetic Gag expression cassette; 3) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag expression cassette; 4) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag expression cassettes in mice by using intramuscular and subcutaneous routes.

The disclosure further claims that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag expression cassette.

The as-filed specification provides sufficient guidance for one skilled in the art to make an immunogenic composition comprising an expression cassette comprising of SEQ ID NO: 3 or 4 (and SEQ ID NO: 1 or 2) and for one skilled in the art to use a plasmid comprising the claimed cassette in a method of producing an immune response in a mammal by using i.m. administration of the plasmid.

However, the as-filed specification does not provide sufficient description or factual evidence for one skilled in the art to make and/or use a sequence having at least 90% identity to any of the sequences presented as SEQ ID NO: 1-4 other than the sequences themselves. The specification does not provide sufficient guidance for what amino acids of any of the sequences listed above may be changed while the Gag polypeptide activity is retained. In view of the state of the art describing the function of HIV-1 Gag proteins in the virus life cycle as exemplified by Freed, where Freed states that, "the role played by HIV-1 Gag proteins during the life cycle are numerous and complex, involving not assembly but also virion maturation after particle release and early post-entry steps in virus replication". Also, since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have at least 90% sequence identity to the Gag polypeptide encoded by SEQ ID NOs: 1-4 and still possess HIV Gag polypeptide activity.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 1-4, does not reasonably provide enablement for a polynucleotide sequence encoding a polypeptide including

an immunogenic HIV Gag polypeptide, wherein the polynucleotide sequence encoding said Gag polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 1, 2, 3 or 4. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing nucleotide sequences encoding a HIV Gag polypeptide with 90% sequence identity to the claimed SEQ ID NOs. In addition, the prophetic examples as provided in the specification do not reasonably extrapolate to the full scope of the claimed invention.

Applicant's arguments filed 8/28/03 have been fully considered but they are not found persuasive.

With respect to applicants' argument that, "Applicants are under no legal obligation to teach each and every member of a claimed genus" and "at least six representative species are described (SEQ ID NOs: 1-4, 20 and 21)," the argument is not found persuasive. The argument is not found persuasive because SEQ ID NO: 1 is a fragment of SEQ ID NO: 3 and SEQ ID NO: 2 is a fragment of SEQ ID NO: 4. Claim 1 recites a nucleotide sequence having at least 90% sequence identity to the sequence presented as either SEQ ID NO: 1 or SEQ ID NO: 2. In other words, the sequence claims may be larger than either SEQ ID NO: 1 or 2. Claims 1-4 are broader than the enabling disclosure because there is no guidance as to which (if any) of the 497 amino acids (estimated amino acids for SEQ ID NO: 3) or 503 amino acids (estimated amino acids for SEQ ID NO: 4) may be changed while HIV Gag activity is retained and the HIV Gag

polypeptide is still immunogenic. The total number of 500 amino acid peptides is $1.13 \times 10^{66}$. The number of single amino acid substitutions is 9,500. The number of two amino acid substitutions is over 90,000,000. A nucleotide search of SEQ ID NO: 4 (1509 nucleotides) indicates that SEQ ID NO: 3 (1479 nucleotides) is 84.6% identical. The same nucleotide search of SEQ ID NO: 4 indicates that it has 98.7% sequence identity to SEQ ID NO: 21 and 83.6% sequence identity to SEQ ID NO: 20. Furthermore, the specification contemplates that a nucleic acid sequence encodes an immunogenic Gag polypeptide and further wherein the nucleic acid sequence comprises a nucleic acid sequence having at least 90% sequence identity to the sequence presented in either nucleotides 844-903 of SEQ ID NO: 3 or nucleotides 841-900 of SEQ ID NO: 4. However, other than the nucleic acid sequences of SEQ ID NO: 3 and 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) or SEQ ID NO: 4 (SEQ ID NO: 2); and SEQ ID NO: 20 and 21, the specification fails to disclose any other nucleic acid with Gag activity. The specification provides no guidance as to which (if any) of the nucleotides or amino acids may be changed while Gag activity is retained. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473,

2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997).

Furthermore, with respect to the argument that, "Applicants are under no legal obligation to teach each and every member of a claimed genus." The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using the claimed genus of polynucleotide sequences, for those skilled in the art to experiment with polynucleotide sequences having 90% identity to the SEQ ID NOs: 1-4 and are immunogenic and retain Gag activity as intended by the as-filed specification at the time the invention was made.

With respect to applicants' argument that, "the reference (Ngo, supra) cited in the 112 first paragraph enablement rejection is not relevant to the claimed subject matter" and "Sequences that do not produce immunogenic Gag polypeptides are not encompassed by the claims," the argument is not found persuasive. The specification provides no guidance as to which (if any) of the nucleotides or amino acids may be changed while Gag activity is retained. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or

amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997).

Furthermore, with respect to applicants' arguments that, "Sequences that do not produce immunogenic Gag polypeptides are not encompassed by the claims", the argument is not found persuasive. The argument is not found persuasive because there are polynucleotide sequences that produce immunogenic Gag polypeptides that are not encompassed by the claims. SEQ ID NO: 3 and 4 are immunogenic as taught by the specification, however, a nucleotide search of SEQ ID NO: 3 against SEQ ID NO: 4 indicates that SEQ ID NO: 4 does not have at least 90% sequence identity to SEQ ID NO: 3. In view of the definition of immunogenic in the specification, any wild-type Gag polypeptide would be considered immunogenic. The prior art teaches two nucleotide sequences encoding an immunogenic HIV Gag polypeptide that are not 90% identical to SEQ ID NO: 4. See US Patent 6,541,248, SEQ ID NOs: 2 and 5.

With respect to applicant's argument that, "the cases cited are not applicable," the argument is not found persuasive. The argument is not found persuasive because Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 teaches that even though the specification is not required to disclose each and every species, there must be sufficient guidance to for one skilled in the art to make and use the claimed invention as broadly case. This is the case here. In view of the In Re Wands Factors, the specification does not teach one skilled in the art how to make and use the full scope of the claimed invention. The art of record teaches the problem with predicting a function of a protein by using nucleotide sequence alignment programs. The specification provides no guidance as to which (if any) of the nucleotides or amino acids may be changed while HIV Gag activity is retained. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997).

The declaration under 37 CFR 1.132 filed 12/19/02 is insufficient to overcome the rejection of claims 1-10, 24-43, 49-60, and 62-66 based upon 112 enablement as set forth in the instant Office action because: in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use the full scope of the claimed invention.

Furthermore, a nucleotide sequence search of SEQ ID NO: 4 (1509 nucleotides) indicates that SEQ ID NO: 3 (1479 nucleotides) is 84.6% identical to SEQ ID NO: 4. The same nucleotide search indicates that it has 98.7% sequence identity to SEQ ID NO: 21 and 83.6% sequence identity to SEQ ID NO: 20. The prior art teaches two nucleotide sequences encoding an immunogenic HIV Gag polypeptide that are not 90% identical to SEQ ID NO: 4. See US Patent 6,541,248, SEQ ID NOs: 2 and 5. There is a substantial variation between species of immunogenic HIV Gag polypeptides. Furthermore, the specification contemplates that a nucleic acid sequence encodes an immunogenic Gag polypeptides and further wherein the nucleic acid sequence comprises a nucleic acid sequence having at least 90% sequence identity to the sequence presented in either nucleotides 844-903 of SEQ ID NO: 3 or nucleotides 841-900 of SEQ ID NO: 4. However, other than the nucleic acid sequences of SEQ ID NO: 3 and 4 and fragments of SEQ ID NO: 3 (SEQ ID NO: 1) or SEQ ID NO: 4 (SEQ ID NO: 2); and SEQ ID NO: 20 and 21, the specification fails to disclose any other nucleic acid with immunogenic Gag activity. The specification provides no guidance as to which (if any) of the nucleotides or amino acids may be changed while Gag activity is retained. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these

changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al., *Journal of Molecular Biology*, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997).

***Double Patenting***

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 6, 67, and 74-75 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, and 16 of co-pending Application No. 09/899,575. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the claims of co-pending application '575 are drawn to an expression cassette comprising a polynucleotide comprising x contiguous nucleotides, wherein (i) the X contiguous nucleotides have at least 90% identity to Y contiguous nucleotides of SEQ ID NO: 51, 99, or 68 (claims 7, 8,16, respectively). SEQ ID NO: 51 in claim 7 and SEQ ID NO: 99 in claim 8 are 100% identical to SEQ ID NO: 1 in the instant application. In addition, SEQ ID NO: 68 is 100% identical to SEQ ID NO: 2 of the instant application. Furthermore, claims 74 and 75 of the instant application '704 are obvious variants of claims 7, 8, and 16 of co-pending application '575 because the only difference between clams 74-75 of the instant application and claims of co-pending application '575 is using the expression cassette in a composition for producing an immune response in a mammal and a method of using the composition. One of ordinary skill in the art would have concluded that the invention defined in the claims in the application '704 is an obvious variant of the invention defined in the claims of the co-pending application '575.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed 8/28/03 have been fully considered but they are not persuasive. Applicants have not provided a terminal disclaimer to overcome the double patenting rejection.

***Conclusion***

Claims 68-73 are in condition for allowance because they are free of the prior art of record.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

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Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635